P/2107-297

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:	Confirmation No.: 4965
Ferdinand Hermann Bahlmann, et al.	Group Art Unit: 1647
Serial No.: 10/586,896	Examiner: Regina M. Deberry
Filed: October 16, 2006	

For: USE OF LOW-DOSE ERYTHROPOIETIN FOR STIMULATING ENDOTHELIAL PRECURSOR CELLS, REGENERATING ORGANS, AND SLOWING DOWN PROGRESSION OF END ORGAN DAMAGES

VIA EFS-WEB
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

DECLARATION OF PROF. DR.
HERMANN HALLER UNDER 37 C.F.R. §1.132

I, Hermann Haller, hereby declare that:

1. I am a German citizen, residing at An der Trift 8D, 30559 Hannover, Germany. I am a trained Physician and Scientist, working in the field of kidney disease at the university level for several years.
2. I am a co-inventor of application Serial No. 10/586,896 and I am familiar with that application. I have reviewed the Office Action from the United States Patent and Trademark Office mailed August 6, 2009 and I understand the rejections set forth therein. I am making this declaration in support of the patentability of the claims of application Serial No. 10/586,896.
3. I understand that a copy of a professional article, namely, Bahlmann et al., "Low-Dose Therapy With the Long-Acting Erythropoietin Analogue Darbepoetin Alpha Persistently Activates Endothelial Akt and Attenuates Progressive Organ Failure", *Circulation* 2004 (110), pp. 1006-1012 is being provided as an attachment to an Amendment being filed by our U.S. patent counsel in response to the U.S. Examiner's August 6, 2009 Office Action. Both Dr. Ferdinand Hermann

Bahlmann and I, who are the named co-inventors of the present invention and application, are identified as co-authors of the subject publication.

4. The article does not explicitly state that the rats treated by the methodology described therein exhibited a dysfunction of endothelial progenitor cells, i.e., as required in the pending claims 54 and 57 of the present patent application. The following discussion is thus provided to demonstrate that, in fact, the rats treated as described in the Bahlmann et al journal article (page 1007, left hand column, second section) actually did suffer from a reduced number of endothelial progenitor cells ("EPC's"), i.e., in addition to a cardiovascular risk and end-organ damage – as recited in claim 54 (as amended) of the present application.

5. By me and Dr. Jan Menne , a series of experiments was carried out **in 2009** as described below to demonstrate the effect of low-dose darbepoetin (i.e., an EPO derivative) on the number of endothelial progenitor cells circulating in the systemic blood supply of the subjects tested. The experimental protocol and the results achieved thereby are as set forth in Attachment A to this declaration entitled, "Low-dose darbepoetin treatment has beneficial effect on EPC's in the 5/6 nephrectomy model".

6. The data provided in Attachment A constitutes a comparison of the endothelial progenitor cell (EPC) count in a first group (Group 1) of mice having no renal disease and a second group (Group 2) of mice having an experimentally induced renal disease. The mice of Group 2 having the renal disease which represent the mice whose treatment was described in Bahlmann et al. (page 1007, left hand column, second section) accordingly display a low number of EPC's, which evidences that the mice used as patients in Bahlmann et al. suffer from a EPC dysfunction. The mice of Group 3, having the same disease and symptoms as the rats of the placebo-treated Group 2 rats, were, treated with EPO at a low dose (i.e., 20 IU EPO/kg body wt./week which is equivalent to 0.1 μg darbepoetin /kg body wt./week), following which treatment the treated rats of Group 3 demonstrated an increase in the number of EPC's. This additional data, therefore, taken in conjunction with the data presented in Bahlmann et al., provides additional evidence that in a group of subjects subject to the symptoms a), b) and

c) as recited in the present claims, acute or chronic renal failure may be successfully treated by the addition to low, i.e., subpolycythemic dosage(s) of EPO of 1 to 90 IU EPO/kg of body wt./week.

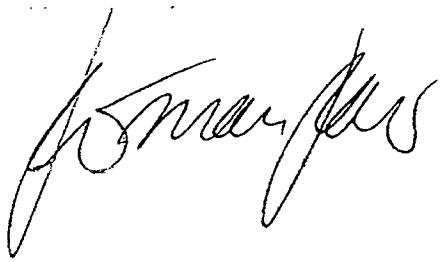
7. Further to the above, as also discussed in the Amendment accompanying this declaration, by me and Dr. Jan Menne a further series of experiments was carried out wherein the method of the claimed invention was carried out on human patients suffering from acute or chronic renal failure and exhibiting a) a reduced number of endothelial progenitor cells (i.e., a dysfunction of the endothelial progenitor cells), b) high blood pressure (a cardiovascular risk factor) and c) a reduced kidney function (i.e., at least one end-organ damage). The experimental method and the results thus obtained are as set forth in Attachment B to this declaration. In the manner explained in further detail below, treatment of the indicated subjects with low-dosage EPO, i.e., 30 and 83 IU/kg body wt./week, led to a significant increase in the number of endothelial progenitor cells. This increase was, therefore, found to act to repair and regenerate damaged renal tissue, thus leading to the treatment of acute or chronic renal failure as recited in the presently pending claims.

8. I turn, now to a discussion of the data presented in Attachment B, wherein the successful treatment of the human patients is substantiated. The Examiner's attention is respectfully directed to Figure 1 which shows a quantitative determination of cultivated endothelial progenitor cells (EPC's) in (a) healthy subjects and (b) in patients suffering from type II diabetes with hypertension. It can be seen from Figure 1 that the absolute number of endothelial progenitor cells in patients with type II diabetes (with hypertension) is significantly lower than the number found in age and sex-matched healthy control subjects. This evidences that patients with at least one cardiovascular risk factor (i.e., hypertonia) together with end-organ damage (i.e., reduced kidney function), have a lower amount of EPC's, which amount can be elevated – as shown in Figure 2a, below and Example 1 and Figures 1-4 of the present application, by EPO-induced promotion of EPC formation, thus producing positive therapeutic results.

9. Furthermore, the additional experimental data presented in Figures 2a and 2b of Attachment B to this declaration represents the results obtained in two human patients having a diminished number of endothelial progenitor cells, a cardiovascular risk factor, i.e., hypertonia and end-organ damage, i.e., reduced renal function, which were treated with EPO in a dosage of 30 IU/kg body wt./week and 83 IU/kg body wt./week. The treatment resulted in an increase in the amount of endothelial progenitor cells for 2-6 weeks following the commencement of the EPO therapy (see, e.g., Fig. 2a). The amount of endothelial progenitor cells found in these human patients following EPO treatment in accordance with the method recited in present amended claim 54 was found to be equivalent to the amount of endothelial progenitor cells found in healthy control subjects (see, e.g., Fig. 2b). We, however, did not observe such an increase in the amount of endothelial progenitor cells in the control patient, i.e., who was not treated with EPO.

10. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 28-01-2010 By:



Hermann Haller